(1999)); VAST (Gibrat, et al., Curr Opin Struct Biol 6(3):377-385. (1996)); CATH (Orengo, et al., Structure 5(8):1093-1108. (1997)); PhD Predictor (Rost, B. Sander, C., and Schneider, R.,PHD--an automatic mail server for protein secondary structure prediction. Comput Appl Biosci. 1994 Feb;10(1):53-60); Prosite (Hofmann, et al., Nucleic Acids Res 27(1):215-219. (1999)); PIR (Wu CH, Yeh LS, Huang H, Arminski L, Castro-Alvear J, Chen Y, Hu Z, Kourtesis P, Ledley RS, Suzek BE, Vinayaka CR, Zhang J, Barker WC The Protein Information Resource. Nucleic Acids Res. 2003 Jan 1;31(1):345-7); GenBank; PDB (H. M. Berman, T. Battistuz, T. N. Bhat, W. F. Bluhm, P. E. Bourne, K. Burkhardt, Z. Feng, G. L. Gilliland, L. Iype, S. Jain, P. Fagan, J. Marvin, D. Padilla, V. Ravichandran, B. Schneider, N. Thanki, H. Weissig, J. D. Westbrook and C. Zardecki, Acta Cryst., The Protein Data Bank (2002). D58, 899-907); and BIND (Bader, et al., Nucleic Acids Res 29(1):242-245. (2001)).

C1

*Please replace the paragraph found on page 8, lines 1-12 with the following rewritten paragraph.*

Similarly, structural alignment of structurally related proteins can be done to generate sequence alignments. There are a wide variety of such structural alignment programs known. See for example VAST from the NCBI (Gibrat, et al., Curr Opin Struct Biol 6(3):377-385. (1996); SSAP (Orengo and Taylor, Methods Enzymol 266(617-635 (1996)) SARF2 (Alexandrov, Protein Eng 9(9):727-732. (1996)) CE (Shindyalov and Bourne, Protein Eng 11(9):739-747. (1998)); (Orengo et al., Structure 5(8):1093-108 (1997); Dali (Holm et al., Nucleic Acid Res. 26(1):316-9 (1998), all of which are incorporated by reference). These sequence alignments can then be examined to determine the observed sequence variations. Libraries can be generated by predicting secondary structure from sequence, and then selecting sequences that are compatible with the predicted secondary structure. There are a number of secondary structure prediction methods such as helix-coil transition theory (Munoz and Serrano, Biopolymers 41:495, 1997), neural networks, local structure alignment and others (e.g., see in Selbig et al., Bioinformatics 15:1039-46, 1999).

C2

*Please replace the paragraph found on page 12, lines 12-16 with the following rewritten paragraph.*

Similarly, residues which may be chosen as variable residues may be those that confer undesirable biological attributes, such as susceptibility to proteolytic degradation, dimerization or aggregation sites, glycosylation sites which may lead to immune responses, unwanted binding activity, unwanted allostery, undesirable enzyme activity but with a preservation of binding, etc. In the present invention, it is the oligomerization domain residues which are varied, as outlined below.

**Title:**

Please replace the title with the following replacement title.

**Novel TNF-alpha variants**

**In the Drawings:**

Please replace Figure 8 with the substitute Figure 8 herein provided.

Please replace Figure 9 with the substitute Figure 9 herein provided.

Replace Figure 10A with substitute Figure 10A.

## REMARKS

Claims 1-3 and 13-16 are pending in this application.

Objection to Specification:

With respect to the Specification, all embedded hyperlinks and/or other forms of browser-executable code have been removed. References to publications for PhD Predictor, PIR, PDB and VAST have been added to provide support for their use as examples. A typographical error has been correct on page 12, lines 12-16. Line 16, now recites "oligomerization," instead of "tetramerization." Support for this amendment may be found in the Specification at page 23, lines 1-2, and lines 20-27. Applicants submit no new matter has been added by this amendment.

Objection to Title:

The title of the invention has been changed to "Novel TNF-alpha Variants," to more clearly indicate the claimed invention.

Objection to Drawings: